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DOI: 10.1371/journal.ppat.1001176 · Source: [PubMed](#)[Cite this publication](#)**Aartjan te Velhuis**

32.04 · University of Cambridge

**Sjoerd van den Worm**

27.73 · Oregon Health and Science University

**Amy C Sims**[+ 2](#)**Ralph S Baric**

46.56 · University of North Carolina at Chapel Hill

[Show more authors](#)

## Abstract

Increasing the intracellular Zn(2+) concentration with zinc-ionophores like pyrithione (PT) can efficiently impair the replication of a variety of RNA viruses, including poliovirus and influenza virus. For some viruses this effect has been attributed to interference with viral polyprotein processing. In this study we demonstrate that the combination of Zn(2+) and PT at low concentrations (2  $\mu$ M Zn(2+) and 2  $\mu$ M PT) inhibits the replication of SARS-coronavirus (SARS-CoV) and equine arteritis virus (EAV) in cell culture. The RNA synthesis of these two distantly related nidoviruses is catalyzed by an RNA-dependent RNA polymerase (RdRp), which is the core enzyme of their multiprotein replication and transcription complex (RTC). Using an activity assay for RTCs isolated from cells infected with SARS-CoV or EAV—thus eliminating the need for PT to transport Zn(2+) across the plasma membrane—we show that Zn(2+) efficiently inhibits the RNA-synthesizing activity of the RTCs of both viruses. Enzymatic studies using recombinant RdRps (SARS-CoV nsp12 and EAV nsp9) purified from *E. coli* subsequently revealed that Zn(2+) directly inhibited the *in vitro* activity of both nidovirus polymerases. More specifically, Zn(2+) was found to block the initiation step of EAV RNA synthesis, whereas in the case of the SARS-CoV RdRp elongation was inhibited and template binding reduced. By chelating Zn(2+) with MgEDTA, the inhibitory effect of the divalent cation could be reversed, which provides a novel experimental tool for *in vitro* studies of the molecular details of nidovirus replication and transcription.

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### Project

#### Role of the influenza A virus RNA polymerase in pathogenicity

● Aartjan te Velthuis

Find out why the RNA polymerase directly contributes to viral pathogenicity and virulence. Find out how an RNA polymerase of a pandemic virus contributes to virulence.

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#### Norovirus

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### Project

#### Pathogenesis of arbovirus infections

● Byron Martina · Ab D. M. E. Osterhaus · ● Chantal B. E. M. Reusken · [...] · Joost C M Meijers

The project focuses on understanding the pathogenesis of mosquito and tick-borne viruses, like dengue, Zika, West Nile, Japanese encephalitis, yellow fever, and tick-borne encephalitis.

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